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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,795	08/16/2001	Rima Rozen	04844/005005	3757

21559 7590 03/26/2003

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	6

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,795	ROZEN, RIMA	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/738,000* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, i.e., methods for selecting a therapy for a subject suffering from a psychosis.

2. Claims 29-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) methods for identifying individuals in need of therapy for schizophrenia by detecting the presence of a C to T mutation at position 677 of the MTHFR gene, (ii) methods of identifying individuals with schizophrenia that have an increased likelihood of responding to neuroleptic therapy by detecting individuals who are homozygous for the T allele at position 677 of the MTHFR gene and (iii) methods of treating individuals for schizophrenia by detecting the presence of a C to T mutation at position 677 of the MTHFR gene and administering to those patients that are homozygous for the T allele a neurolepic medication, does not reasonably provide enablement for methods of selecting a therapy for a subject suffering from any type of psychosis wherein the methods detect any mutation in the MTHFR gene or for research methods which determine whether a mutant MTHFR allele is associated with the safety or efficacy of a type of treatment for psychosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for selecting a therapy for a subject suffering from a psychosis wherein said methods comprise analyzing the MTHFR nucleic acid in a sample from said subject and detecting the presence of a MTHFR mutant allele in said subject as indicative of the safety or efficacy of treatment. The claims further include methods of determining whether a mutant MTHFR allele is associated with the safety or efficacy of a treatment for psychosis and methods of preventing, delaying or treating a psychosis by detecting a MTHFR allele and determining a preferred therapy. In particular, the psychosis is schizophrenia and the method detects a mutation at position 677 in addition to another MTHFR mutant allele. Firstly, it is noted that the claims are drawn broadly to include the selection of therapy for any type of psychosis. As defined in the specification (page 18), a psychosis may include, for example, schizophrenia, manic-depressive disease, psychosis in alcohol or drug intoxication, post-infection psychosis, senile psychosis and acute idiopathic psychotic illnesses. Additionally, the specification (page 22) indicates that the presence of a MTHFR mutant allele may be used to evaluate any therapy for a psychotic disorder in terms of its safety, efficacy (i.e., ability to ablate, reduce or stabilize symptoms or prevent the onset of symptoms in subjects at risk of the psychotic disorder) or toxicity (e.g., reduced pharmacological or physiological effects).

However, the claims are not commensurate in scope with the enabling disclosure because, while the specification teaches an association between homozygosity for the 677T allele and

responsiveness to neuroleptic therapy in schizophrenic patients, the specification has not adequately taught one of skill in the art how to predictably select therapies for any type of psychosis by detecting any mutation in the MTHFR gene without undue experimentation. In particular, the specification (see, for example, table 2) discloses several missense and splice site mutations in the MTHFR gene which result in decreased activity and/or decreased thermal stability of the encoded MTHFR protein. The specification also teaches that a block in methyltetrahydrofolate leads to elevated homocysteine levels and that high plasma levels of homocysteine may be a risk factor for some types of pathological conditions, including mental retardation, seizures and psychiatric disturbances. Data is provided in the specification showing that the homozygous and heterozygous C677T mutations were found more frequently in schizophrenia patients than in controls (pages 79-82). The specification also teaches that schizophrenic patients homozygous for the 677T allele are more likely to respond to neuroleptic treatment (see page 82 and Table 9). However, the specification does not teach or provide sufficient guidance to identify additional mutations in the MTHFR gene that are associated with schizophrenia or other types of psychosis or response to treatments for these conditions without undue experimentation. While the specification contemplates that other types of psychiatric disorders may be associated with elevated plasma homocysteine levels and thereby may be associated with the presence of MTHFR mutations, the specification provides no data to support the hypothesis that MTHFR mutations are correlated with the occurrence of psychosis in general. No evidence has been provided to show that all forms of psychosis are correlated with MTHFR

mutants or that all forms of psychosis are associated with reduced MTHFR activity. There are also no teachings in the specification or art which establish a universal correlation between increased homocysteine levels and the occurrence of MTHFR mutant alleles. That is, it has not been established that MTHFR mutant alleles are present in all psychosis in which increased plasma homocysteine have been observed. In fact, the teachings in the art indicate that other forms of neuropsychiatric disorders are not associated with MTHFR mutant alleles. For example, Zuliani (Acta Neurol Scand (2001) 103: 304-308) states that while subjects with the MTHFR C677T mutant allele have moderately increased plasma homocysteine levels, the C677T mutation has not been found to be associated with AD, cognitive impairment, or vascular dementia (see page 306). Gussekloo et al (Journal of Neurology, Neurosurgery, and Psychiatry (1999) 67: 535-538) also teaches that the MTHFR C677T mutation is not correlated with dementia in persons 85 years and over. Chapman (Stroke (1998) 29: 1401-1404; cited in the IDS of August 16, 2001) also reports that the MTHFR C677T mutation is not associated with vascular dementia or Alzheimer's disease. The ability to establish a correlation between a mutation and a response to therapy is highly unpredictable, even in circumstances in which the effect of the mutation (e.g., decreased enzyme activity or thermostability) has been determined. Furthermore, the specification is also not enabling for methods which detect any mutation other than the C677T mutation as indicative of response to treatment for schizophrenia. The specification teaches "disease causing" mutations in the MTHFR gene can be identified by detecting those mutations which result in decreased activity of the encoded MTHFR protein. The specification does not teach any other

types of mutations which are "indicative of MTHFR deficiency". It is highly unpredictable as to what other types of alterations in the MTHFR gene would be associated with psychosis or schizophrenia and could be used to select treatment for psychosis or schizophrenia. No specific guidance is provided in the specification as to how to predictably identify additional mutations in the MTHFR gene which could be used to diagnose psychosis or schizophrenia. In fact, the teachings of the specification suggest that benign polymorphisms are not associated with disease and therefore could not be used to predict a patients response to treatment. For example, the specification which teaches that the T1317C allele is likely a benign change. Accordingly, it does not appear that benign polymorphisms, particularly the T1317C polymorphism, could be used to select therapy for any type of psychosis or for schizophrenia.

As discussed above, the claims are inclusive of methods of identifying therapies that can be used to delay or prevent the onset of psychosis. The specification (page 58) indicates that individuals that are homozygous for the C677T mutation may benefit from folic acid supplementation. As discussed in the specification, higher levels of plasma folate may lead to normalization of homocysteine levels in individuals having this MTHFR mutation and may prevent the occurrence of disorders associated with high levels of homocysteine. However, the specification has not established that any type of therapy could be used to delay/prevent the onset of schizophrenia or psychosis. The specification has disclosed only that individuals that are homozygous for the 677T allele are more likely to be responsive to neuroleptic treatment. The specification does not identify any alleles that are associated with toxicity or safety of therapy and

it is also highly unpredictable as to how the presence of 677T allele or any other MTHFR allele could be associated with toxicity and safety of therapy. It is highly unpredictable as to how a mutation in a gene will effect drug responsiveness in general. The specification provides no guidance as to how to identify additional types of drug responsiveness which are associated with MTHFR mutations.

With respect to claims 37-44, the specification is not enabling for methods of determining whether a MTHFR allele is associated with response to therapy. Such methods constitute research methods in which the sole purpose of the method is to evaluate a MTHFR allele and determine whether such an allele is correlated with the safety or efficacy of some type of therapy. It is highly unpredictable as to which alleles in the MTHFR gene would be correlated with response to therapy. The showing of one allele that is associated with response to neuroleptic medications in patients with schizophrenia is not commensurate in scope with the breadth of the claims which analyze any allele of the MTHFR gene and try to determine if one or more of these alleles is associated with responsiveness to therapy in any patient having psychosis.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the

amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art indicates that only the homozygosity for the 677T MTHFR allele is correlated with responsiveness of schizophrenia patients to neuroleptic treatment. Furthermore, the state of the art indicates that in general it is highly unpredictable as to how a particular mutation will effect drug responsiveness unless there is a specific correlation between the effect of the mutation and the activity of the drug. In the absence of a specific correlation between a mutation and drug activity, mutations which are correlated with drug responsiveness can only be identified by randomly searching the MTHFR gene for genetic alterations and trying to determine whether these mutations alter the responsiveness or toxicity to any drug. Such random, trial by error experimentation is considered to be undue. Accordingly, in view of the high level of unpredictability in the art and the lack of information and guidance provided in the specification regarding an association between schizophrenia and other MTHFR mutations, regarding an association between MTHFR and other forms of psychosis, and regarding MTHFR mutations and response to treatment for psychosis, undue experimentation would be required to practice the invention as it is broadly claimed.

3. Claims 29-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-44 are indefinite. Claims 29-36 are drawn to a method for selecting a therapy for a subject suffering from a psychosis. However, the final step of the method is one for detecting a mutant allele as indicative of the safety or efficacy of said therapy. The claims do not set forth the relationship between selecting a therapy and detecting the presence of an allele that is indicative of safety or efficacy. Thereby, it is unclear as to whether the claims are intended to be limited to methods which in general select a therapy or methods which identify or select therapies that are safe or efficient. Similarly, claims 37-44 are indefinite because it is not clear as to whether the claims are intended to be limited to methods for determining whether a mutant MTHFR allele is indicative of a response to a therapy or if the claims are intended to be limited to methods for determining if a mutant MTHFR allele is indicative of the safety or efficacy of therapy.

Claims 34-35, 42-44 and 50-52 are indefinite over the recitation of "subject comprises at least two MTHFR mutant alleles" because it is not clear as to whether it is merely a property of the subjects that are being analyzed that they have at least 2 mutations in the MTHFR allele or whether the method includes an actual step of analyzing for the presence of at least 2 mutations in the MTHFR gene and determining a therapy based on the presence of the stated 2 mutations.

Claims 45-52 are indefinite over the recitation of "preferred therapy". While the claims include a step of determining a MTHFR allele that is predictive of the safety or efficacy of an anti-psychotic therapy, the claims do not clarify how one determines a preferred therapy. That is, the claims do not clearly sate the criteria for determining which therapy is preferred.

4.

Priority

It is noted that the claims are entitled only to the filing date of June 12, 2000. While the parent applications disclose methods for detecting a mutant MTHFR allele and methods for identifying patients with MTHFR deficiency, the parent applications do not specifically disclose methods for selecting a therapy for a subject suffering from psychosis or schizophrenia. The parent applications also teach that the mutant MTHFR alleles may be associated with neurological disorders and psychiatric disorders. However, the genus encompassed by neurological and psychiatric disorders is very large and these general teachings in the parent applications do not provide basis for the specific embodiments claimed of selecting a therapy for a subject suffering from psychosis and schizophrenia.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 29-33 and 37-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Joober Molecular Psychiatry (May 2000) 5: 323-326; cited in the IDS of January 21, 2003).

It is noted that the inventive entity of the present application is distinct over the authorship of the Joober et al reference. This rejection may be overcome by the filing of a 132 Katz-type declaration, if appropriate.

Joober et al (see for example, page 325) disclose methods for identifying MTHFR mutant alleles associated with response to therapy in schizophrenic patients wherein the methods comprise identifying individuals who are responsive and non-responsive to therapy, analyzing the MTHFR nucleic acids of said individuals for the presence of a MTHFR allele and determining whether the mutant allele is associated with responsiveness to therapy. The reference teaches that the presence of the 677T MTHFR allele was significantly higher in schizophrenia patients responsive to neuroleptics versus controls (see, for example, page 323). With respect to claims 29-33, the method steps recited by Joober are identical to those set forth in the present claims. That is, Joober teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. Further, the recitation of "wherein the presence of said mutant allele is indicative of the safety or efficacy of said therapy" is considered to be a property that is inherent to the detected MTHFR mutant allele. Alternatively, such a recitation is considered to be a mental step.

6. Claims 29-33 and 37-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Joober et al (Molecular Psychiatry (September 1999) 4: 515-516; cited in the IDS of August 16, 2001).

It is noted that the inventive entity of the present application is distinct over the authorship of the Joober et al reference. This rejection may be overcome by the filing of a 132 Katz-type declaration, if appropriate.

Joober et al disclose methods for identifying MTHFR mutant alleles associated with response to therapy in schizophrenic patients wherein the methods comprise identifying individuals who are responsive and non-responsive to therapy, analyzing the MTHFR nucleic acids of said individuals for the presence of a MTHFR allele and determining whether the mutant allele is associated with responsiveness to therapy. The reference teaches that the presence of the 677T MTHFR allele (referred to therein as the "V allele") was significantly higher in schizophrenia patients responsive to neuroleptics versus controls. With respect to claims 29-33, the method steps recited by Joober are identical to those set forth in the present claims. That is, Joober teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. Further, the recitation of "wherein the presence of said mutant allele is indicative of the safety or efficacy of said therapy" is considered to be a property that is inherent to the detected MTHFR mutant allele. Additionally, such a recitation is considered to be a mental step.

7. Claims 29-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Arinami (American Journal of Medical Genetics (1997) 74: 526-528; cite din the IDS of August 16, 2001).

Arinami (page 526-527) disclose methods for identifying MTHFR mutant alleles in schizophrenic patients wherein the methods comprise analyzing the MTHFR nucleic acids of said individuals for the presence of a MTHFR allele and determining the presence of a mutant MTHFR allele. The reference teaches that individuals that are homozygous for the 677T MTHFR allele

are significantly more likely to have schizophrenia as compared to controls. It is a property of the 677T allele that it is associated with response to neuroleptic therapy in schizophrenic patients. Arinami (see page 527) also teaches that individuals that are homozygous for the 677T allele have mild MTHFR deficiency and mild hyperhomocysteinemia and that an association between the 677T allele and schizophrenia will allow for the effective initiation of preventive and therapeutic measures in carriers of this allele. The method steps recited by Arinami are identical to those set forth in the present claims. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. Further, the recitation of "wherein the presence of said mutant allele is indicative of the safety or efficacy of said therapy" is considered to be a property that is inherent to the detected MTHFR mutant allele. Additionally, such a recitation is considered to be a mental step.

8. Claims 29-33, 37-41 and 45-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Regland et al (Journal of Neural Transmission (1997) 104: 931-941).

Regland et al provide the results of a study establishing a correlation between the presence of the thermolabile MTHFR C677T allele (referred to therein as "TL-MTHFR") and the occurrence of schizophrenia. The reference teaches that presence of the T allele was significantly higher in hyperhomocysteinemic schizophrenia patients versus controls (see, for example, page 935-936). Regland (page 934) also teaches methods for detecting the presence of the C677T mutation in nucleic acid samples from patients. It is stated that "(w)e suggest that homozygosity for TL-MTHFR be regarded as a vulnerability factor in the pathogenesis of the schizophrenic

syndrome, i.e. a factor that increases the risk of developing schizophrenia " (see page 938). In particular, Regland teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. With respect to claims 29-33, the method steps recited by Regland are identical to those set forth in the present claims. That is, Regland teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. Further, the recitation of "wherein the presence of said mutant allele is indicative of the safety or efficacy of said therapy" is considered to be a property that is inherent to the detected MTHFR mutant allele. Additionally, such a recitation is considered to be a mental step. With respect to claims 37-41, the method of Regland comprises determining the response of schizophrenic patients to folate supplementation and vitamin B12, analyzing the MTHFR nucleic acids in a sample obtained from schizophrenics, and determining the presence of a MTHFR mutant allele, namely the 677T allele, that is correlated with response to therapy. Regland reports that individuals homozygous for the 677T MTHFR allele did not respond to B12 but were normalized by folate supplementation, whereas in individuals homozygous for the C677 MTHFR allele, homocysteine concentrations were reduced by vitamin B12 alone. With respect to claims 45-49, Regland teaches that the risk of schizophrenia may be reduced by folate supplementation and teaches methods that include the steps of analyzing the MTHFR nucleic acids in a sample,

determining the presence of a C677T MTHFR mutation, determining a preferred therapy and administering a preferred therapy.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joober et al (May 2000).

Joober et al (see for example, page 325) disclose methods for identifying MTHFR mutant alleles associated with response to therapy in schizophrenic patients wherein the methods comprise identifying individuals who are responsive and non-responsive to therapy, analyzing the MTHFR nucleic acids of said individuals for the presence of a MTHFR allele and determining whether the mutant allele is associated with responsiveness to therapy. The reference teaches that the presence of the T allele was significantly higher in schizophrenia patients responsive to neuroleptics versus controls (see, for example, page 323). Joober does not exemplify methods of

selecting a therapy for patients with schizophrenia by detecting the presence of the T allele at position 667 of the MTHFR gene, does not specifically teach administering a preferred therapy to patients carrying the 677T allele and does not teach detecting 2 or more MTHFR mutations. However, in view of the teachings of Joober of an association between the T allele and increased responsiveness to therapy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have developed a method of selecting a therapy for a subject suffering from schizophrenia by assaying for the presence of the T allele in order to have provided an effective and rapid means for identifying individuals more likely to respond to neuroleptic treatment. Furthermore, in view of the teachings of Joober it would have been obvious to one of ordinary skill in the art to have analyzed other known mutations in the MTHFR gene for the association with response to therapy in order to have identified additional mutations that could be used for screening patients for their response to therapy. With respect to claims 45-52, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have treated those patients having the 677T allele with neuroleptics since Joober teaches that such individuals would be more likely to be responsive to this type of treatment.

10. Claims 29-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joober et al (September 1999).

Joober et al disclose methods for identifying MTHFR mutant alleles associated with response to therapy in schizophrenic patients wherein the methods comprise identifying individuals who are responsive and non-responsive to therapy, analyzing the MTHFR nucleic

acids of said individuals for the presence of a MTHFR allele and determining whether the mutant allele is associated with responsiveness to therapy. The reference teaches that the presence of the 677T MTHFR allele (referred to therein as the "V allele") was significantly higher in schizophrenia patients responsive to neuroleptics versus controls. Joober does not exemplify methods of selecting a therapy for patients with schizophrenia by detecting the presence of the T allele at position 667 of the MTHFR gene, does not specifically teach administering a preferred therapy to patients carrying the 677T allele, and does not teach detecting 2 or more MTHFR mutations. However, in view of the teachings of Joober of an association between the T allele and increased responsiveness to therapy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have developed a method of selecting a therapy for a subject suffering from schizophrenia by assaying for the presence of the T allele in order to have provided an effective and rapid means for identifying individuals more likely to respond to neuroleptic treatment. Furthermore, in view of the teachings of Joober it would have been obvious to one of ordinary skill in the art to have analyzed other known mutations in the MTHFR gene for the association with response to therapy in order to have identified additional mutations that could be used for screening patients for their response to therapy. With respect to claims 45-52, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have treated those patients having the 677T allele with neuroleptics since Joober teaches that such individuals would be more likely to be responsive to this type of treatment.

11. Claims 29-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arinami.

Arinami (page 526-527) disclose methods for identifying MTHFR mutant alleles in schizophrenic patients wherein the methods comprise analyzing the MTHFR nucleic acids of said individuals for the presence of a MTHFR allele and determining the presence of a mutant MTHFR allele. The reference teaches that individuals that are homozygous for the 677T MTHFR allele are significantly more likely to have schizophrenia as compared to controls. It is a property of the 677T allele that it is associated with response to neuroleptic therapy in schizophrenic patients. Arinami (see page 527) also teaches that individuals that are homozygous for the 677T allele have mild MTHFR deficiency and mild hyperhomocysteinemia and that an association between the 677T allele and schizophrenia will allow for the effective initiation of preventive and therapeutic measures in carriers of this allele.

Arinami does not exemplify methods of selecting a therapy for patients with schizophrenia by detecting the presence of the T allele at position 667 of the MTHFR gene, does not specifically teach administering a preferred therapy to patients carrying the 677T allele and does not teach detecting 2 or more MTHFR mutations. However, in view of the teachings of Arinami of an association between the T allele and increased likelihood of schizophrenia and the teachings of Arinami of an association between individuals homozygous for the 677T allele and hyperhomocysteinemia, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have developed a method of selecting a therapy for a subject suffering from schizophrenia by assaying for the presence of the T allele in order to have provided an effective and rapid means for identifying individuals more likely to require treatment for

hyperhomocysteinemia and for schizophrenia. Furthermore, in view of the teachings of Arinami, it would have been obvious to one of ordinary skill in the art to have analyzed other known mutations in the MTHFR gene for an association with schizophrenia and response to therapy in order to have identified additional mutations that could be used for screening patients for their likelihood of having schizophrenia and their response to therapy for schizophrenia and to hyperhomocysteinemia. With respect to claims 45-52, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have treated those patients having the 677T allele with preventive or therapeutic measures or with agents for the treatment of hyperhomocysteinemia since Arinami teaches that such individuals homozygous for the 677T allele have an increased risk of having hyperhomocysteinemia and should be given preventive and therapeutic measures for schizophrenia.

12. Claims 29-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regland et al (Journal of Neural Transmission (1997) 104: 931-941).

Regland et al provide the results of a study establishing a correlation between the presence of the thermolabile MTHFR C677T allele (referred to therein as "TL-MTHFR") and the occurrence of schizophrenia. The reference teaches that presence of the T allele was significantly higher in hyperhomocysteinemic schizophrenia patients versus controls (see, for example, page 935-936). Regland (page 934) also teaches methods for detecting the presence of the C677T mutation in nucleic acid samples from patients. It is stated that "(w)e suggest that homozygosity for TL-MTHFR be regarded as a vulnerability factor in the pathogenesis of the schizophrenic

syndrome, i.e. a factor that increases the risk of developing schizophrenia " (see page 938). In particular, Regland teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. The method steps recited by Regland are identical to those set forth in the present claims. That is, Regland teaches a method comprising analyzing the MTHFR nucleic acid in a sample and determining the presence of at least one MTHFR mutant allele. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. Further, the recitation of "wherein the presence of said mutant allele is indicative of the safety or efficacy of said therapy" is considered to be a property of the 677T allele. Additionally, such a recitation is considered to be a mental step. The method of Regland also comprises determining the response of schizophrenic patients to folate supplementation and vitamin B12, analyzing the MTHFR nucleic acids in a sample obtained from schizophrenics, and determining the presence of a MTHFR mutant allele, namely the 677T allele, that is correlated with response to therapy. Regland reports that individuals homozygous for the 677T MTHFR allele did not respond to B12 but were normalized by folate supplementation, whereas in individuals homozygous for the C677 MTHFR allele, homocysteine concentrations were reduced by vitamin B12 alone. Lastly, Regland teaches that the risk of schizophrenia may be reduced by folate supplementation and teaches methods that include the steps of analyzing the MTHFR nucleic acids in a sample, determining the presence of a C677T MTHFR mutation, determining a preferred therapy and administering a preferred therapy.

Regland does not teach analyzing the MTHFR gene for 2 or more mutant alleles. However, in view of the teachings of Regland of an association between the T allele and increased responsiveness to folate supplementation and increased risk of schizophrenia and the teachings of Regland of additional MTHFR mutants and the association between thermolabile MTHFR and hyperhomocysteinemia (pages 931-932), it would have been obvious to one of ordinary skill in the art to have analyzed the MTHFR gene for other known mutations to determine an association between the mutations and response to therapy in order to have identified additional mutations that could be used for screening patients for their response to therapy. With respect to claims 45-52, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have treated those patients having the 677T allele and other mutant alleles associated with thermolabile MTHFR with folate supplementation since Regland teaches that such individuals would be more likely to be responsive to this type of treatment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 24, 2003

CARLA J. MYERS
PRIMARY EXAMINER